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A 2002 Update: Managing Lipid Disorders

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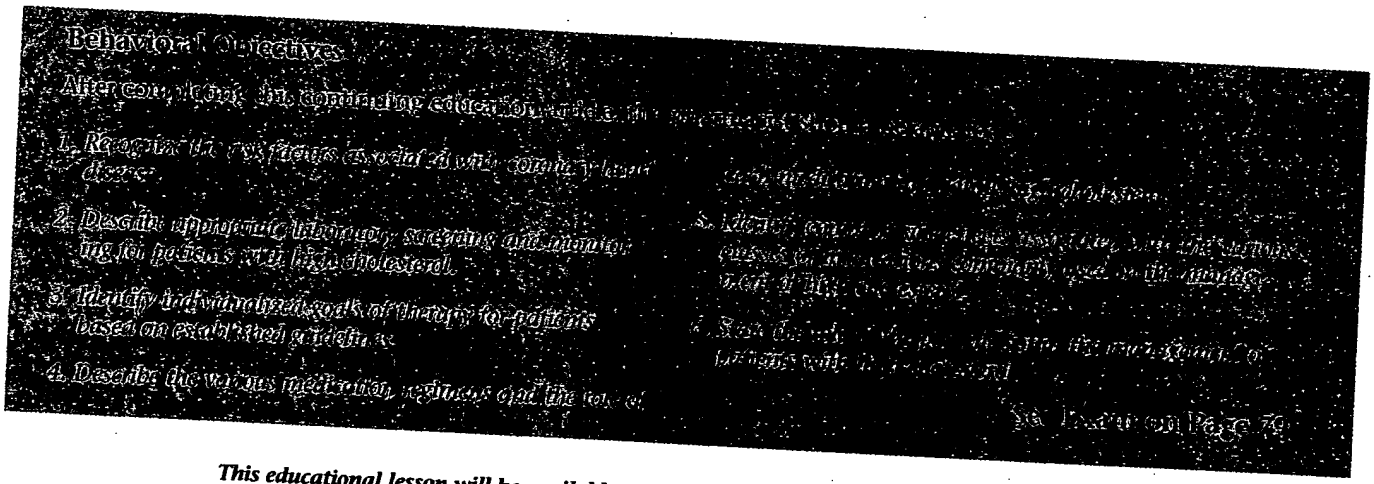

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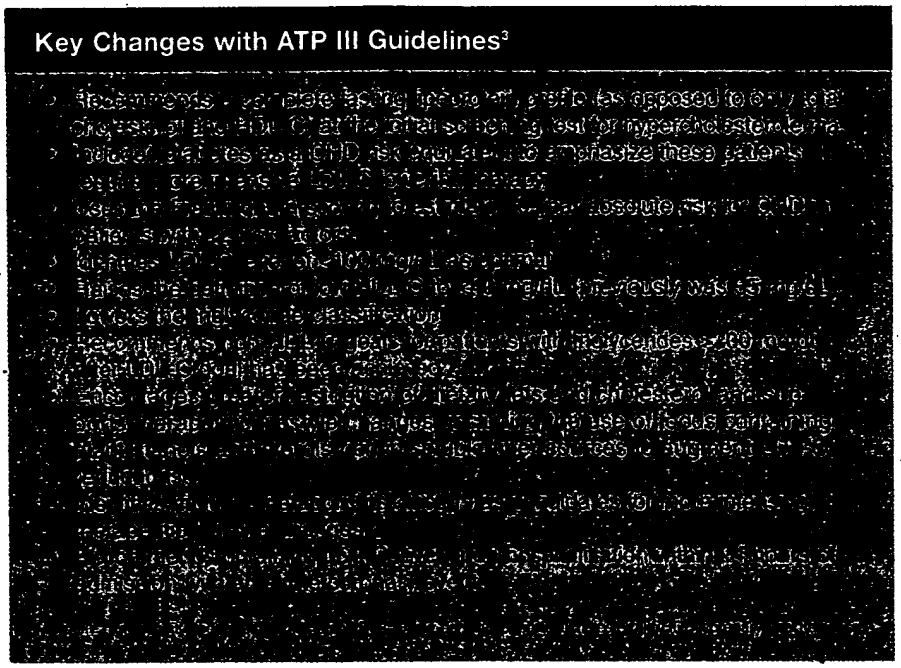
Introduction

Coronary heart disease (CHD) is the leading cause of death in the United States. Approximately 949,000 Americans die each year of this disease, and associated morbidity costs total more than $298 billion annually.[1] The National Cholesterol Education Program (NCEP) developed guidelines aimed at reducing the risk of CHD in patients with lipid abnormalities, with the most recent recommendations issued in 2001.[2,3] In the second guidelines (ATP II), clear objectives were established with treatment goals based largely on low-density-lipoprotein (LDL) cholesterol levels. On the basis of the NCEP goals, an estimated 52 million adults require dietary changes, and 12.7 million need lipid-lowering therapy.[4] Despite the well-established relationship between lipid abnormalities and CHD morbidity and mortality,[5-14] there is a significant void between NCEP guidelines and clinical practice with respect to managing patients at risk for CHD. The third iteration of the NCEP guidelines (ATP III) released in May 2001 provides further insight into dyslipidemia and the management of patients at risk for CHD. All health care providers who routinely come in contact with patients being treated for dyslipidemias should become familiar with the new ATP III guidelines (www.nhlbi.nih.gov).[3] Table 1 provides an overview of the changes (from ATP II) in the new ATP III guidelines.

Recent studies suggest that management including lipid-lowering therapy is not achieving NCEP LDL target levels in large portions of dyslipidemic patients.[15,16] The Lipid Treatment Assessment Project (L-TAP study), conducted in the primary care setting,

Table 1

Key Changes with ATP III Guidelines[3]



showed that therapy achieved target LDL values in 38% of patients; for patients without CHD, success rates were 68% among low-risk patients (fewer than two CHD risk factors) and 37% among high-risk patients (two or more CHD risk factors). Patients with CHD had the lowest success rate of 18% (Figure 1).[15] Another study demonstrated that while patients had been identified at being at risk for CHD in the primary care setting, only 35.5% had a decrease in their calculated CHD risk after being treated for dyslipidemia. The authors conclude more aggressive management of patients is warranted in achieving target lipid levels and reducing the risk for CHD.[16]

Undertreatment of dyslipidemia is not limited to a lack of drug therapy. Studies indicate that patients receiving lipid-lowering medications can also be inadequately treated.[17-19] In two Veterans Administration medical center studies, lipid-lowering therapy resulted in patients achieving NCEP-established LDL goals in only 33% to 50% of patients.[17,18] Health care providers are not solely responsible for the low success rates for meeting NCEP goals. Patient compliance is typically poor.[20] Results from one study revealed that only 38% of patients remained on their lipid-lowering therapy after 12 months.[21]

Pharmacists managing lipid-lowering treatment have demonstrated improvement in patient compliance and persistence.[22] In Project ImPACT (Improved Persistence and Compliance with Therapy), pharmacist-directed care was provided to 397 patients with hyperlipidemia in 26 community pharmacies. Patients complied with their lipid-reduction strategies 94% of the time in this project, and they persisted with medication therapy 90% of the time. More importantly, this study showed that lipid management by pharmacists produced better NCEP LDL goal outcomes than any previously published national study of patients with dyslipidemia. Among patients with existing CHD, 48% met their NCEP LDL goals, whereas 67% of patients without CHD met their target, and overall 63% of patients achieved goal by the end of the study (Figure 1).

Increased attention has been given to community and ambulatory care pharmacists providing care to patients with lipid abnormalities, but opportunities also exist in the hospital setting. A multidisciplinary approach led by pharmacists at one hospital was designed and implemented to improve outcomes in patients with coronary artery disease.[23] The percentage of patients receiving lipid-lowering therapy on discharge increased from a baseline value of 40% to a range of 72% to 81%.

NCEP ATP III Guidelines

Risk Factors

The NCEP recommends that the intensity of treatment for individual patients depends on risk status.[2,3] Risk factors for CHD, other than elevated cholesterol levels, are listed in Table 2. To determine a patient's risk status, add one point for each positive risk factor, and then subtract one risk factor if the patient has an elevated high-density-lipoprotein (HDL) cholesterol level (≥60 mg/dL). Risk factors for CHD are considered modifiable and nonmodifiable. Age and family history are nonmodifiable risk factors, whereas smoking, hypertension, and diabetes are modifiable risk factors. Obesity is not considered an independent risk factor because it operates

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through other risk factors, such as physical inactivity, but they should be considered targets for intervention.

Laboratory Screening and Monitoring

New to ATP III is the recommendation that all adults ≥20 years of age should be screened for hyperlipidemia at least once every 5 years (Table 3)[2,3,24] with a complete fasting lipoprotein profile (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides). Initial classification of cholesterol and triglyceride concentrations for adults without evidence of CHD are listed in Table 4.

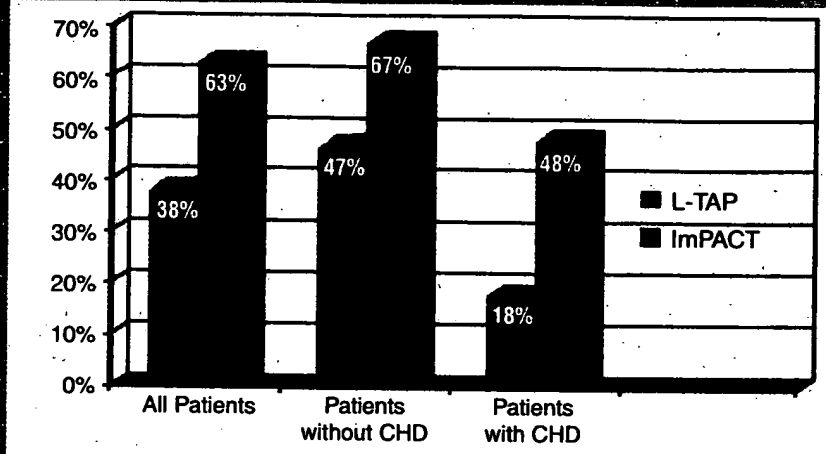
The LDL value can be estimated from the lipid profile using the Friedewald equation: LDL = Total cholesterol – [HDL + (triglycerides/5)].[3] If the triglyceride value is greater than 400 mg/dL, the equation is not accurate and direct LDL measurement should then be used. Patients should fast for ≥9 to 12 hours to measure lipid profiles because plasma triglyceride concentrations are affected by recent food intake, which will affect the calculation of LDL. A convenient way to measure a total lipid profile is the Cholestech LDX Analyzer, a point-of-care laboratory instrument that measures lipid profiles for determination of LDL values within 5 minutes of obtaining a blood sample by fingerstick. The availability of efficient and reliable lipid profile results allows the pharmacist to be directly involved in the management of lipid-lowering therapies.[22]

Treatment Guidelines

Therapeutic lifestyle changes (TLCs) are the foundation of hyperlipidemia treatment. All patients should begin dietary modification and regular exercise while attempting to alleviate any modifiable risk factors for CHD (eg, smoking, hypertension).[2,3,25-30] The threshold LDL levels above which diet and TLCs should be initiated, when to begin drug therapy, and the goals of therapy, are outlined in Table 5.[2,3,31,32]

Figure 1

Percentage of Patients Attaining NCEP Goals from L-TAP and Project ImPACT Studies



NCEP = National Cholesterol Education Program; L-TAP = Lipid Treatment Assessment Project; ImPACT = Improved Persistence and Compliance with Therapy.

The target serum LDL concentration is <160 mg/dL for patients with no risk factors or only one risk factor, <130 mg/dL for patients with two or more risk factors, and <100 mg/dL for those with CHD.[2,3,31,32] Patients with any form of clinically evident atherosclerosis, such as peripheral or carotid vascular disease, should be treated as if they have CHD.[2,3]

Persons with diabetes also fall in this third category, even if they have no apparent cardiovascular disease.[33] Type 2 diabetes is associated with a twofold to fourfold excess risk of CHD, and patients with diabetes also have a higher fatality rate once they have CHD.[33] Drug therapy is not recommended for premenopausal women and men <35 years of age unless they

Table 2

Risk Factors for Coronary Heart Disease[3]

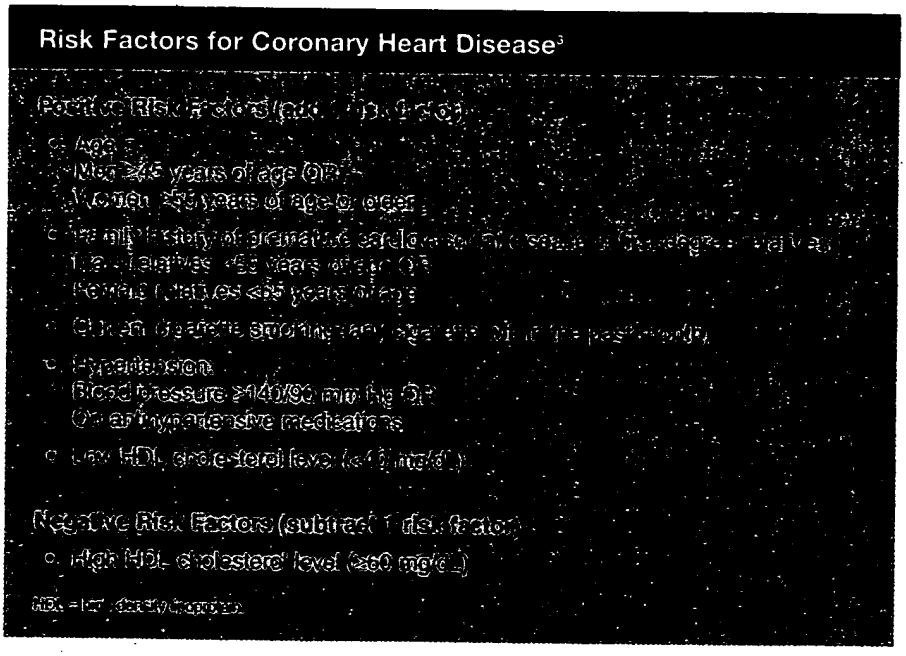
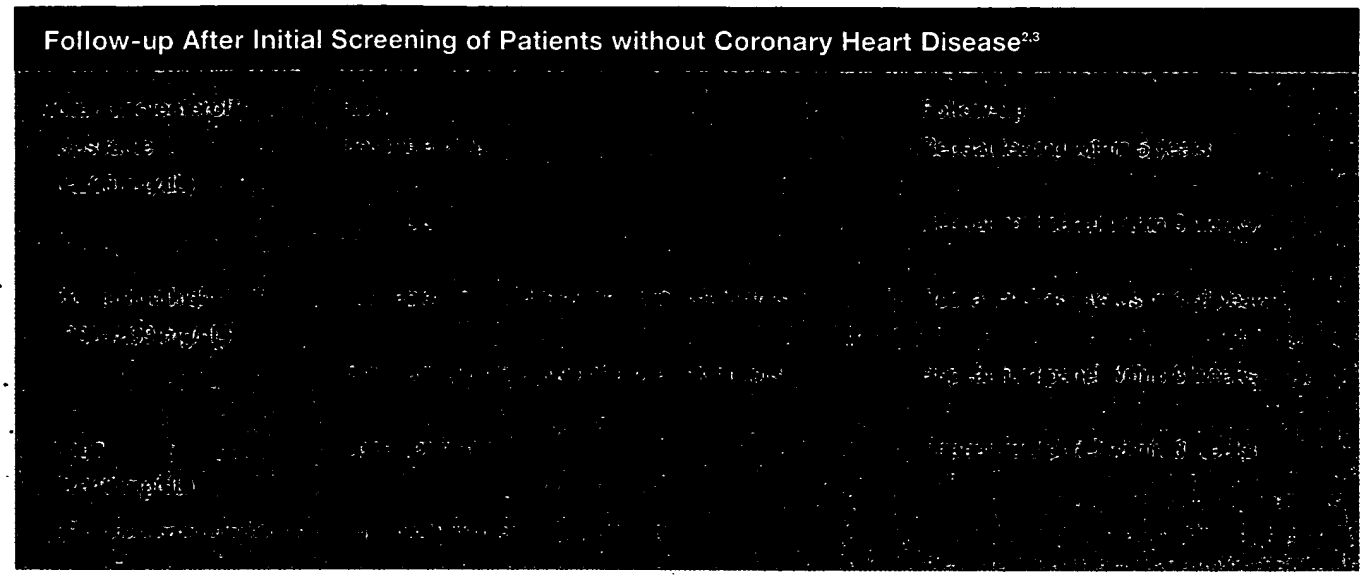


Table 3

Follow-up After Initial Screening of Patients without Coronary Heart Disease[2,3]



have serum LDL levels >220 mg/dL, because their immediate risk of heart disease is low.[2,3] The presence of risk factors and a family history of disease could lower this threshold.

Increasing data demonstrate that high triglyceride and/or low HDL levels are risk factors for CHD, but the primary atherogenic lipoprotein is LDL, and high LDL levels remain the main target for lipid-lowering therapy.[2,3,34-40] One study (VA-HIT) suggested that the rate of coronary events in men is reduced by raising HDL levels and lowering triglyceride levels without lowering LDL cholesterol levels. A 6% increase in HDL was associated with a 22% reduction in major cardiac events.[40]

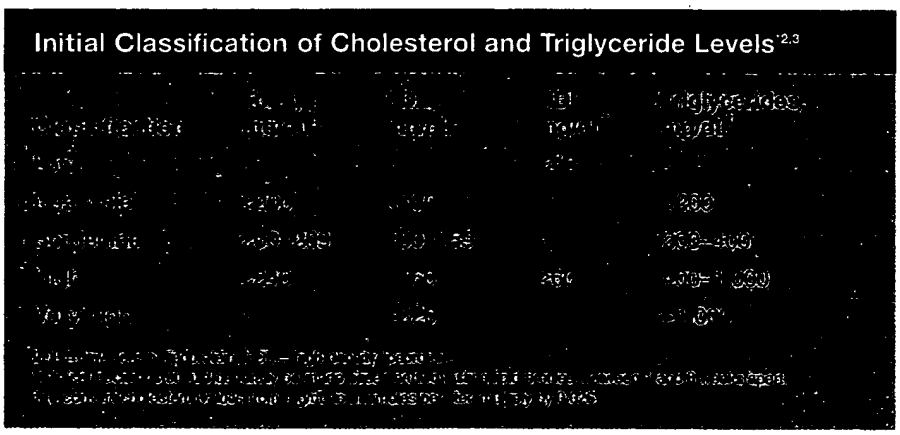
Based on evidence suggesting that triglyceride levels are an independent risk factor for CHD, ATP III reduced the triglyceride classification end points. The revised classification for patients with elevated serum triglyceride levels rely primarily on lifestyle modifications (Table 6).[2,3] The new ATP III recommendations suggest that the primary aim of therapy in patients with hypertriglyceridemia is to achieve appropriate LDL cholesterol goal, in conjunction with reducing triglyceride levels.

Secondary Causes of Hyperlipidemia

Many conditions can cause hyperlipidemia, including obesity, diabetes, hypothyroidism, obstructive liver disease, and nephrotic syndrome.[41] In general, underlying conditions should be treated before lipid-lowering therapy is introduced. Several medications can also cause changes in lipid concentrations, including protease inhibitors, glucocorticoids, alcohol, oral estrogen, and isotretinoin (Table 7).[25,41] Medications with adverse effects on serum lipids may need to be discontinued. It is important to note, however, that the effects may only be mild or transient, and that the benefits of the medication may outweigh any potential increased risk of CHD.

Table 4

Initial Classification of Cholesterol and Triglyceride Levels[2,3]

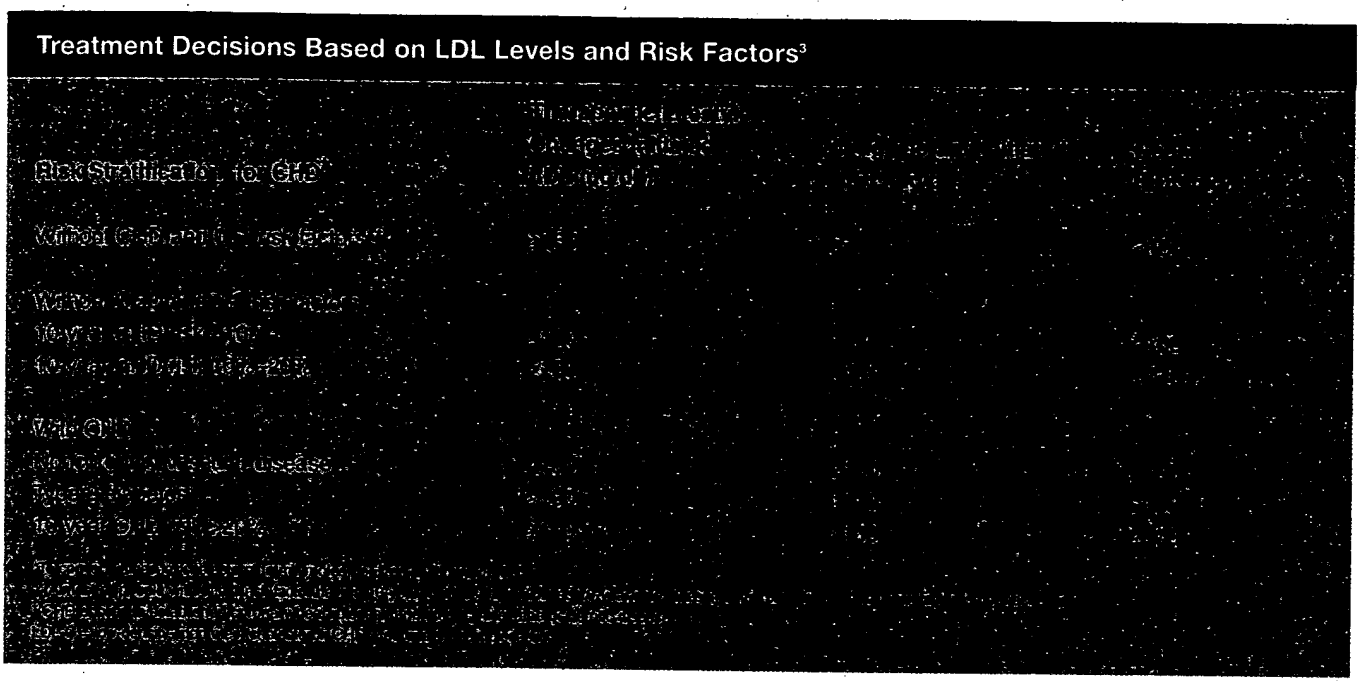


Medication Therapies

Presently, the primary medications used to treat hyperlipidemia are HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (statins), niacin, bile acid resins (BARs), and fibric acid derivatives (Table 8). Of these agents, statins are the most effective at lowering LDL cholesterol, have relatively few adverse effects, and are supported by favorable outcome studies (Table 9).[9-13,17,19] Successful implementation of NCEP guidelines frequently requires multiple lipid-lowering medications because many patients with dyslipidemia have difficulty reaching treatment goals with monotherapy.[17] If further reductions in LDL are required,

Table 5

Treatment Decisions Based on LDL Levels and Risk Factors[3]



combinations of medications should be used, such as the use of niacin and BARs.[2,3] Poorly tolerated regimens decrease patient compliance and persistence, which ultimately affects the achievement of LDL goal values.[17] Patient education by pharmacists can improve medication adherence.

Statins

The statins are competitive inhibitors of HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis.[42] The currently available statins are atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), and simvastatin (Zocor). Cerivastatin (Baycol), manufactured by the Bayer Corp., was withdrawn from the U.S. market on Aug. 8, 2001. Postmarketing surveillance revealed safety concerns of rhabdomyolysis (resulting in severe muscle weakness and organ complications) and confirmed fatalities led to the decision to discontinue all strengths of the product by the company.

Clinical Outcomes with Statins

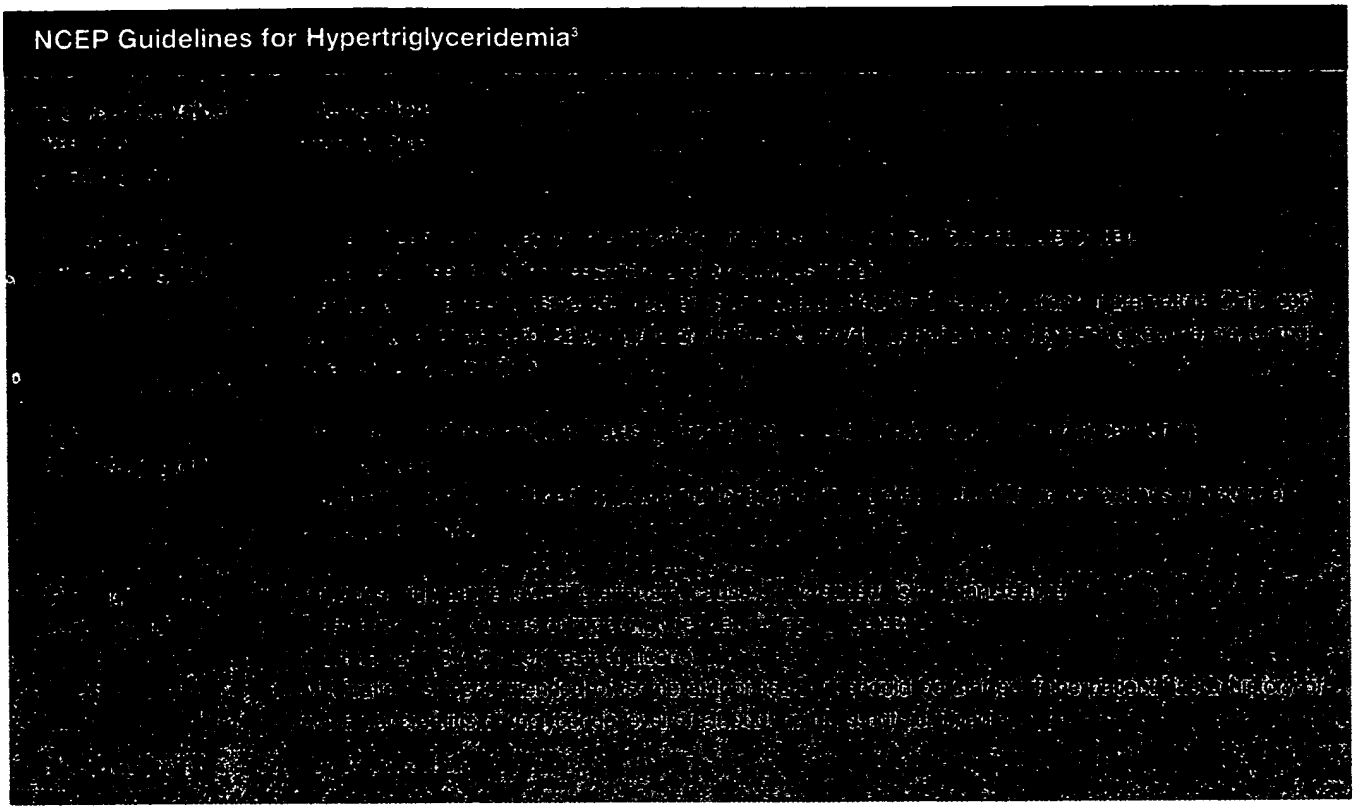
For pharmacists to be more effective in managing lipid disorders and communicating with other health care professionals, it is important to thoroughly understand the major clinical outcomes in statin treatment trials (Table 9). Initial studies of statin therapy examined the impact on coronary artery disease progression and regression.[43] Subsequent large trials with statins demonstrated efficacy, safety, and favorable outcomes.[9-13] These studies provide evidence that statin therapy reduces the risk of first-time (primary prevention) and recurrent (secondary prevention) coronary events and death from all causes. Several of the trials also suggest that statins are capable of reducing ischemic stroke risk by approximately one third in patients with evidence of CHD.[44,45]

The Scandinavian Simvastatin Survival Study (4S) group provided the first evidence that lipid-lowering therapy reduced all-cause mortality in subjects with a history of CHD.[9] This study also demonstrated reduction in coronary death, coronary events, and stroke. In the Cholesterol and Recurrent Events (CARE) study, a secondary prevention trial with pravastatin in men and women with normal cholesterol, risk of coronary death and stroke were both significantly reduced.[11] The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study proved a reduction in mortality, coronary events, and stroke in men and women with evidence of CHD and a wide range of cholesterol levels.[12] The West of Scotland Coronary Prevention Study (WOSCOPS) tested the effectiveness of statins in primary prevention of CHD.[10] Risk of coronary death was decreased with pravastatin in hypercholesterolemic men with no clinical evidence of CHD. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) study with lovastatin showed significantly reduced risk for first coronary events in men and women without CHD and normal to mildly elevated LDL and low HDL cholesterol levels.[13]

Additional clinical benefits of the statins have been noted, and these may be explained by activities beyond the actual lipid-lowering action, including promotion of atherosclerotic plaque stability, improvement of endothelial dysfunction, and reversal of coagulation and platelet abnormalities.[43] Current evidence indicates that the beneficial action of statins occurs rapidly and may provide important anti-ischemic effects as early as 1 month after starting therapy.[43] Most

Table 6

NCEP Guidelines for Hypertriglyceridemia[3]



recently, possible statin benefits outside of the cardiovascular system have been identified: statin therapy was associated with increased bone mineral density and reduced risk of fractures in several observational studies.[46-49]

Adverse Effects

The statins are generally well tolerated. Mild, transient gastrointestinal disturbances, rash, and headache are more common side effects.[42,50] An increase in plasma aminotransferase activities to more than three times normal occurs in 1% to 2% of patients; symptomatic hepatitis is rare.[50] Myopathy with increases in serum creatine kinase (CK) have been reported with all of the statins, and rarely, rhabdomyolysis and myoglobinuria leading to renal failure have occurred.[51] Hepatic or renal dysfunction, electrolyte disturbances, infections, major trauma, and hypoxia may increase the risk of myotoxicity.[50,51] Patients are also at significantly higher risk for myotoxicity with combined treatment of a statin and niacin or fibrates.[42,52]

The risk of both hepatotoxicity and myotoxicity is dose-related and may increase when medications that inhibit statin metabolism are concomitantly prescribed (Table 10).[50-52] Lovastatin, simvastatin, and atorvastatin are all metabolized by CYP3A4 and serum concentrations can be increased by concurrent use of CYP3A4 inhibitors, such as erythromycin, cyclosporin, itraconazole, nefazodone, and protease inhibitors.[42,50,52] Atorvastatin appears to be less affected by inhibitors of CYP3A4.[50] Fluvastatin is metabolized by CYP2C9 and may interact with other medications metabolized by this isozyme.[42] Pravastatin is metabolized by sulfation and serves as a useful option if cytochrome P-450 drug interactions are a concern.[42,52]

Indications

Statins are useful in treating most of the major types of hyperlipidemia.[52] All of the agents effectively decrease LDL levels and are approved for this use by the FDA (Table 7). Although all statins decrease triglyceride levels to some degree and have a minimal effect on raising HDL, the labeled indications vary. Atorvastatin is the most effective statin at reducing LDL levels; unlike the more extensively studied agents, however, it has not been proved to reduce total mortality.

Dosing and Monitoring

Specific dosing and monitoring guidelines for the statins are provided in Table 11. Higher than usual starting doses are sometimes used if the patient needs an LDL reduction beyond what the recommended starting dose can achieve. As most endogenous cholesterol production occurs at night, single doses of these agents should be administered in the evening.[52]

Patients should be reevaluated after each dosage adjustment or therapeutic intervention. Repeat lipid analysis can be obtained as soon as 4 weeks after initiation or changes in therapy.[2,3] Liver function tests (ie, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) should be monitored at baseline and then periodically dur-

Table 7

Effects of Selected Drugs on Serum Lipids

Drug	Lipid Effects	Comments
Alcohol[35]	Increased TG Increased HDL	
Alpha, blockers[36]	Decreased LDL (slight) Decreased TG (5%–15%) Increased HDL (5%–15%)	Beneficial effects
Amiodarone[35,36]	Increased TG	
Anabolic steroids[35,36]	Increased LDL Decreased HDL	
Beta blockers, non-ISA[36]	Increased TG (20%–50%) Decreased HDL (13%–15%)	Beta$_1$-selective agents have less effect on HDL
Beta blockers, ISA[36]	Increased HDL (9%)	Beneficial effects
Corticosteroids[36]	Increased LDL Increased TG Increased HDL	
Cyclosporine[35,36]	Increased LDL	
Estrogen therapy (PEPI)[37]	Decreased LDL (10%) Increased TG (15%) Increased HDL (9%)	Oral CEE alone
Isotretinoin[35,36]	Increased LDL Increased TG (significant) Decreased HDL	
Metformin[36]	Decreased LDL Increased TG	Beneficial effects
Oral contraceptives[36]	Increased LDL Increased TG Decreased HDL	Effects mild and variable; depends on progestin: estrogen ratio
Progestins[36]	Increased HDL (5%–14%)	Related to androgenic activity
Protease inhibitors[38]	Increased TC Increased TG	
Thiazide diuretics[37]	Increased LDL (2%) Increased TG (15%)	Effect is often transient

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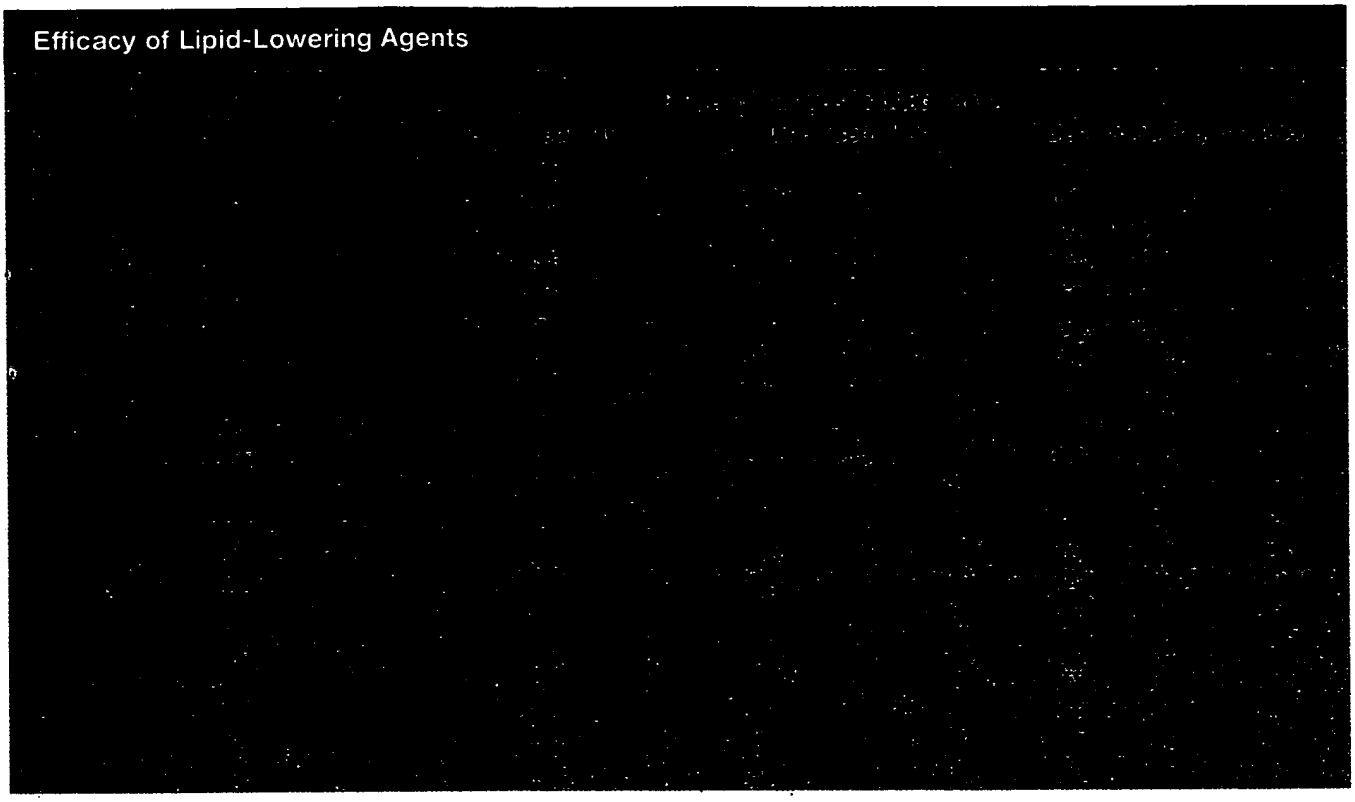
Table 8

Efficacy of Lipid-Lowering Agents



ing therapy.[42] Symptoms of hepatitis induced by statins, including fatigue, abdominal pain, sluggishness, anorexia, and weight loss, resemble those of an influenza-like syndrome.[52] Because CK levels will not rise until muscle pain starts, there is no benefit from periodic testing for myopathy in asymptomatic patients.[42] Although serious adverse effects are rare, patients should be told to discontinue their medication and consult their physician for any unexplained muscle aches or symptoms of hepatotoxicity.

Cost and Cost-Effectiveness

Although the statins are the most expensive lipid-lowering medicines, their use is extremely cost-effective for treating hyperlipidemia in high-risk patients compared with many other routine medical interventions (Table 11).[53,54] Atorvastatin, when compared with simvastatin, lovastatin, and fluvastatin, was found to be the most cost-effective choice to achieve NCEP goals.[55] Primary prevention with a statin may not be cost-effective for younger men and women with few risk factors when compared with primary prevention in older age patients and secondary prevention.[56] This supports the NCEP recommendation that lipid-lowering therapy should be targeted to patients who have CHD or elevated risk for CHD.[2,3]

Niacin (Nicotinic Acid)

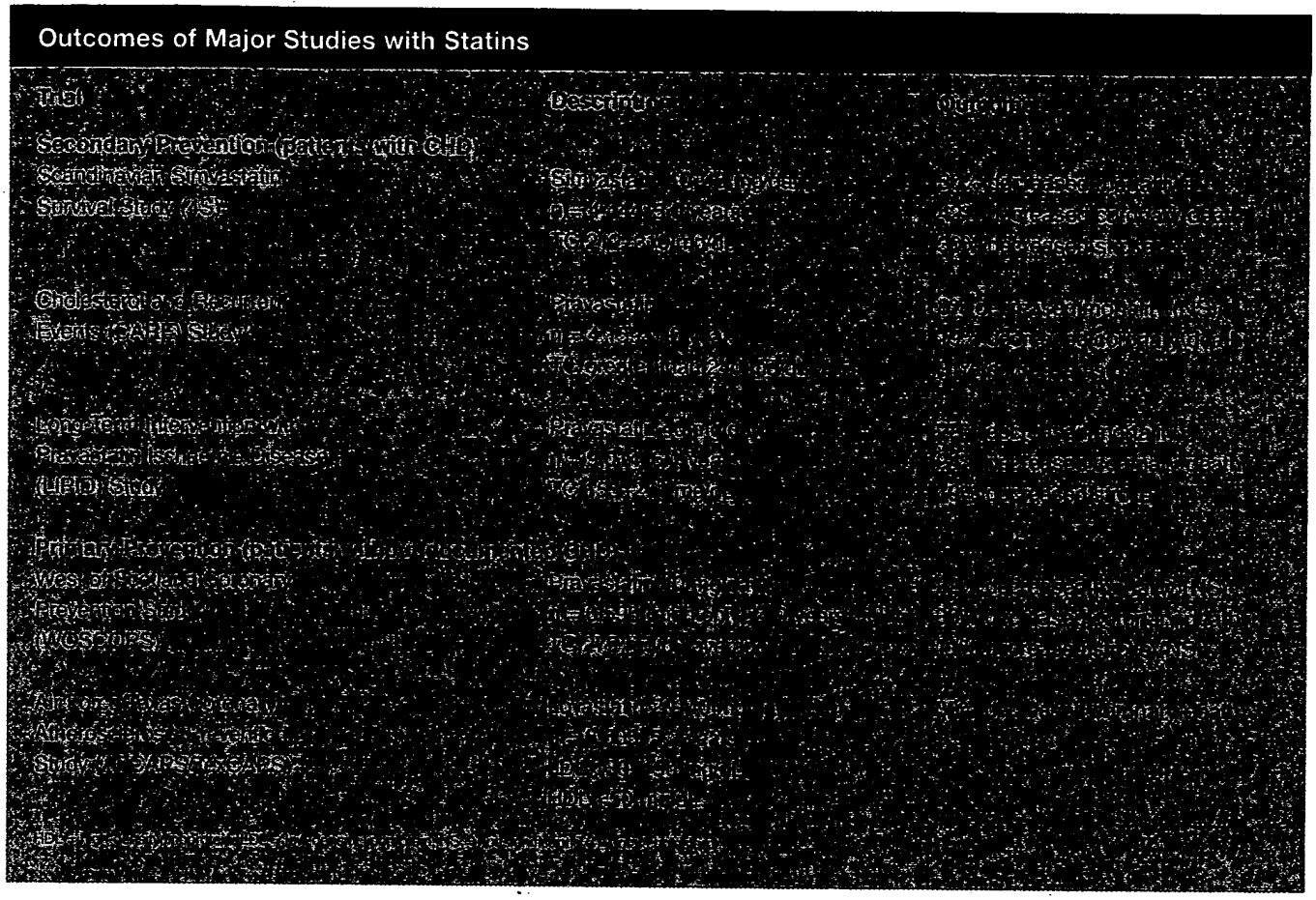
Over the years, niacin has demonstrated clinical efficacy in decreasing LDL and triglyceride levels and more than any other drug, increasing HDL cholesterol (Table 8). It is widely available as an OTC product, but the prescription formulations are most effective in lipid disorders. Niacin has been recommended as a first-line medication for the management of high cholesterol. Immediate-release (IR) crystalline niacin and OTC niacin products have several notable disadvantages, however, mostly relating to poor tolerability, adverse effects, toxicity, and multiple dosing regimens.[57] The clinical effectiveness of IR and unregulated OTC niacin formulations has been limited by their adverse-effect and toxicity profiles, often leading to discontinuation of therapy.

In developing sustained-release formulations to slow the release of niacin, the concern for hepatotoxicity and hepatic enzyme elevations became an issue. The choice was between the flushing with IR niacin and hepatotoxicity with sustained-release formulations.[57] The new extended-release (ER) formulation, once-daily Niaspan, provides a formulation with proven clinical efficacy, enhanced tolerability, a diminished side-effect profile, and convenient dosing. In addition, the new formulation of Niaspan allows for dosing titration that appears better tolerated by patients.[57,58]

In the Coronary Drug Project study, niacin decreased myocardial infarction and 15-year mortality rates in men with CHD.[7] The importance of increasing HDL cholesterol levels to reduce morbidity and mortality has also been demonstrated.[40] A

Table 9

Outcomes of Major Studies with Statins



recent study comparing niacin (Niaspan, 1,000 to 2,000 mg HS) and gemfibrozil (600 mg bid) in patients with low baseline HDL cholesterol levels, revealed that niacin provided up to twofold greater increases in HDL cholesterol and decreases in lipoprotein(a) levels compared with gemfibrozil.[59]

Other recent studies have demonstrated the clinical efficacy of combination therapy of niacin and statins.[60,61] A regimen of slow-release niacin (patients were started on slow-release niacin [Slo-Niacin] but switched to IR niacin due to lack of efficacy) and simvastatin (10 to 20 mg) increased the baseline of HDL by 29% (HDL_2 was 60.5%) and decreased LDL by 43%. More important, the niacin plus statin regimen decreased cardiovascular events by 60% to 90%, as compared with 30% to 35% seen with statin therapy alone. Compliance with the combined regimen of niacin and simvastatin did not differ significantly from the placebo regimen.[60] Niacin either alone or in combination with other lipid-lowering agents (such as statins) warrants further attention in the management of dyslipidemic patients with low baseline HDL cholesterol, based on the favorable changes in LDL and HDL cholesterols, lipoprotein (a), triglycerides, and apolipoprotein A-1.[57-61]

Adverse Effects

The predominant side effects of niacin are secondary to prostaglandin-mediated vasodilation, particularly skin flushing and pruritus.[62] Other side effects include nausea, vomiting, abdominal pain, headache, glucose intolerance, hyperuricemia, exacerbation of peptic ulcer disease, and acanthosis nigricans.[50,62,63] Elevated liver transaminases and hepatitis have been reported with niacin and occur more frequently than in patients taking statins, especially at doses >2,000 mg/day.[52]

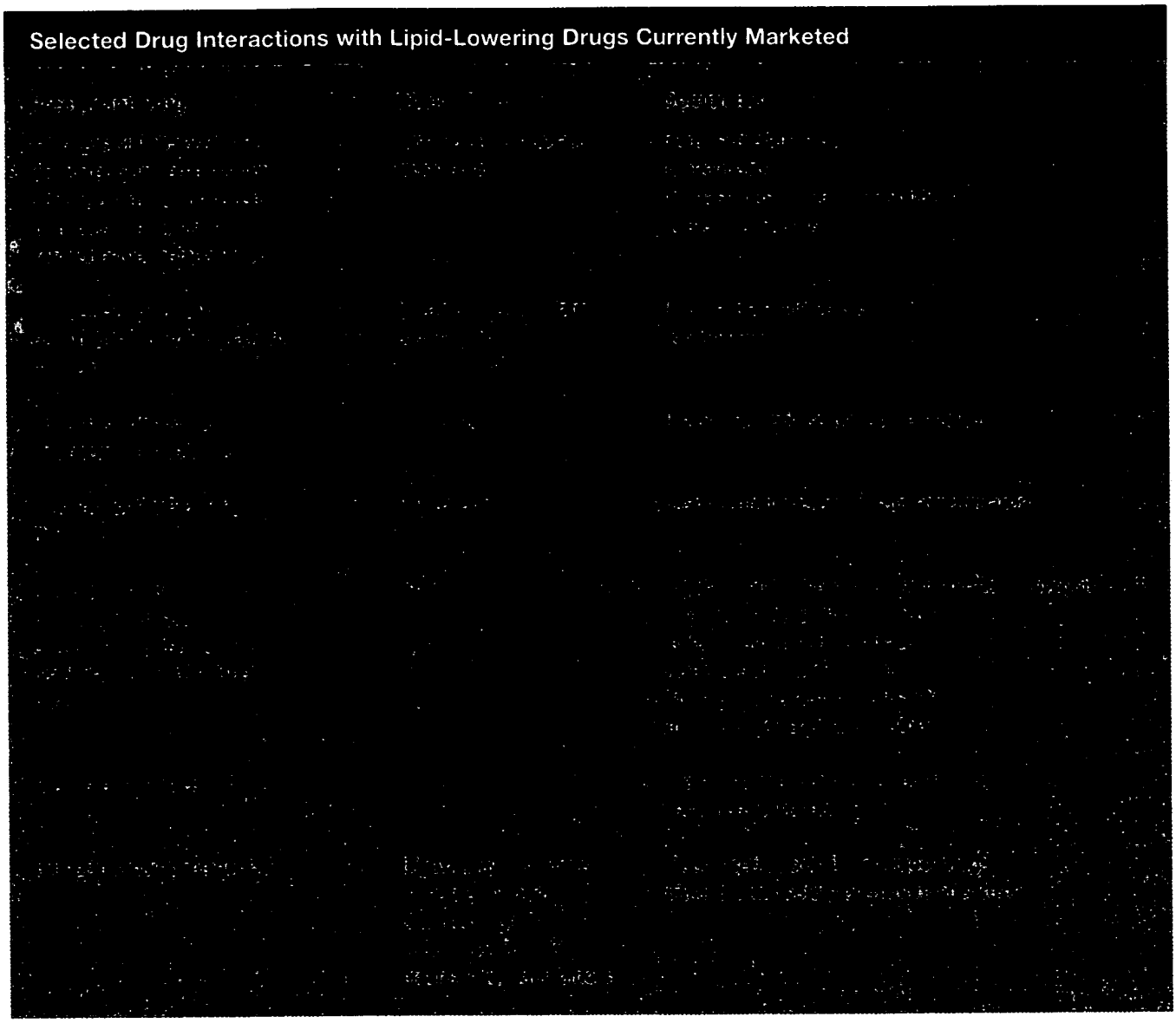
ER and IR niacins have been reported to cause liver dysfunction more commonly than regular-release niacin; but when it is taken at the usual doses this is less of a concern.[50,52,62-64] The ER formulations are also more likely to produce gastrointestinal side effects, but they are generally better tolerated than crystalline IR niacin because they minimize cutaneous flushing.[7,62,63] Patients receiving niacin and statins concomitantly should be monitored for rhabdomyolysis (muscle weakness) and undergo regular liver function tests, especially at the higher dosages.[42,50]

Indications

Niacin is particularly useful for patients with mixed cholesterol

Table 10

Selected Drug Interactions with Lipid-Lowering Drugs Currently Marketed



abnormalities. The ER niacin is often preferred over the regular-release formulations because of improved compliance and persistence secondary to improved tolerability.[50,62] Niacin is no longer believed to be a problem for patients with diabetes but should be used cautiously in patients with a history of peptic ulcer disease, hepatic dysfunction, alcohol abuse, and gout.[50,64]

In December 2001, the FDA approved the first combination product for the treatment of dyslipidemia. The combination of ER niacin and lovastatin (Advicor) offers the advantage of once-daily dosing for the treatment of primary hypercholesterolemia and mixed lipid disorders.[65] This combination may prove helpful and convenient in patients with low baseline HDL and high LDL cholesterols. The new combination product is available in three strengths of ER niacin (500, 750, and 1,000 mg) and lovastatin (20 mg) (Table 10).[65]

Dosing and Monitoring

Side effects of niacin can be minimized by starting at low doses and increasing by small increments (Table 11). Liver function tests (ie, transaminases) should be monitored at baseline and then periodically (every 6 to 12 weeks) during the first year of therapy and thereafter. Serum uric acid and fasting glucose should be tested at baseline and then 4 to 6 weeks after the niacin dosage is stabilized. Patients should be instructed to take 325 mg of aspirin 30 to 60 minutes before each dose of niacin to reduce the severity of flushing. Flushing can be minimized by taking niacin at the end of a meal and not taking it with alcohol or hot beverages. By administering the tablets at nighttime, any flushing that may occur will be mini-

Table 11

Dosing, Monitoring, and Cost* of Lipid-Lowering Agents

Drug	Dosage	Monitoring	Cost[53]
Atorvastatin (Lipitor)	Start: 10 mg daily at bedtime Max: 80 mg daily	Check lipid profile for response at 4 weeks Check ALT/AST at baseline and 12 weeks after starting or dosage increase; then every 6 months Discontinue if ALT or AST is greater than three times normal range or if myopathy or myositis occurs	$55–$94
Fluvastatin (Lescol), (Lescol XL)	Start: 20 mg daily at bedtime Max: 80 mg divided in two daily doses	Check lipid profile for response at 4 weeks Check ALT/AST at baseline and 12 weeks after starting or dosage increase; then every 6 months Discontinue if ALT or AST is greater than three times normal range or if myopathy or myositis occurs	$44–$56
Lovastatin (Mevacor)	Start: 20 mg daily with evening meal Max: 80 mg daily If CrCl is <30 mL/min, maximum daily dose is 20 mg.	Check lipid profile for response at 4 weeks Check ALT/AST at baseline and 12 weeks after starting or dosage increase; then every 6 months Discontinue if ALT or AST is greater than three times normal range or if myopathy or myositis occurs	$66–$237
Pravastatin (Pravachol)	Start: 10 mg daily at bedtime Max: 40 mg daily If hepatic or renal dysfunction, maximum daily dose is 10 mg	Check lipid profile for response at 4 weeks Check ALT/AST at baseline and 12 weeks after starting or dosage increase; then every 6 months Discontinue if ALT or AST > three times normal range or if myopathy or myositis occurs	$70–$107
Simvastatin (Zocor)	Start: 20 mg daily at bedtime Max: 80 mg daily If patient is elderly or has severe renal insufficiency, maximum daily dose is 5 mg If given in combination with fibrates or niacin, maximum daily dose is 10 mg	Check lipid profile for response at 4 weeks Check ALT/AST at baseline and every 6 months for the first year; repeat after dosage increases ALT/AST every 3 months for patients taking 80 mg/day Discontinue if ALT or AST is greater than three times normal range or if myopathy or myositis occurs Closely monitor patients with severe renal insufficiency	$107–$109

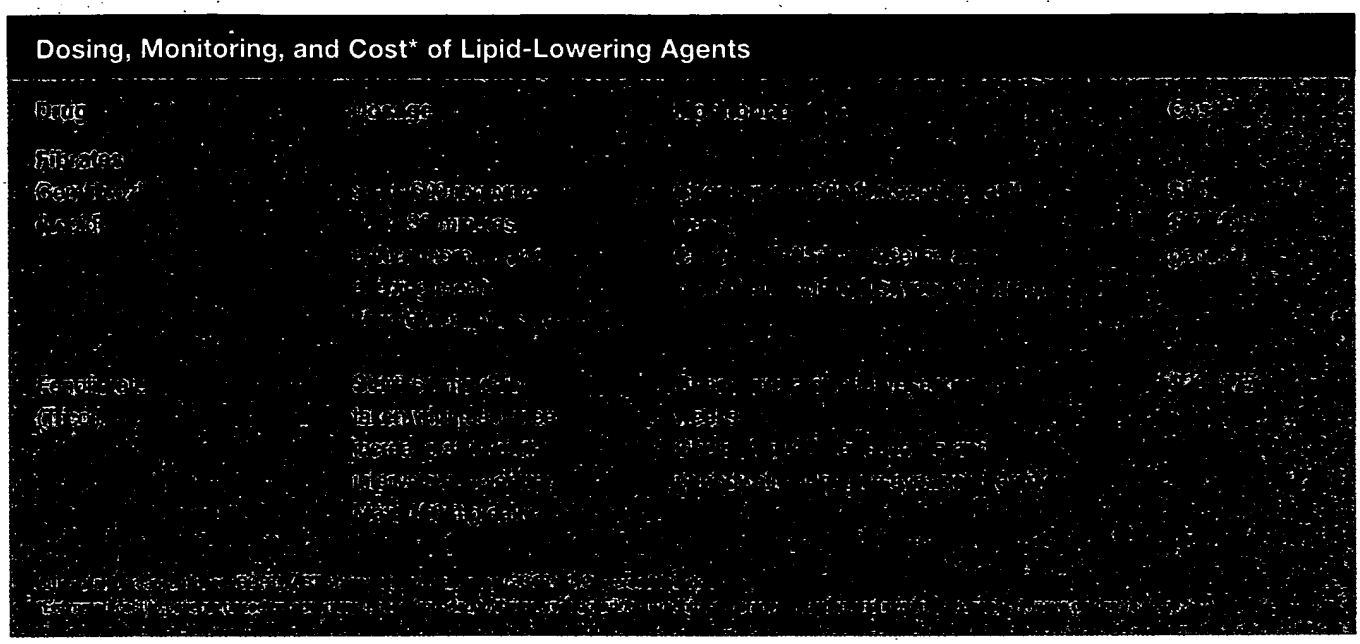
Table 11 *continued*

Dosing, Monitoring, and Cost* of Lipid-Lowering Agents

Drug	Dosage	Monitoring	Cost[52]
Niacin			
Extended-Release Niacin (Niaspan)	Start: 500 mg daily (at bedtime) for 4 weeks, then 1,000 mg daily for 4 weeks; if response inadequate, increase daily dose by 500 mg every 4 weeks, to daily maximum of 2,000 mg Max: 2,000 mg daily	Check lipid profile for response at 4 weeks Check ALT/AST, uric acid, and fasting glucose at baseline and 4 to 6 weeks after the dosage is stabilized[64] Repeat ALT/AST every 12 weeks thereafter for the first year, then every 6 to 12 months[64] Discontinue if ALT or AST is greater than three times normal range or if myopathy or myositis occurs	$24–$80
Nonprescription, Regular-Release Niacin[64]	Start: 50–100 mg twice daily for the first week; double dosage every week to 1,000–1,500 mg/day, in two or three divided doses; if response inadequate, increase dosage slowly to daily maximum of 3,000 mg Max: 3,000 mg daily	Check lipid profile for response at 4 weeks Check ALT/AST, uric acid, and fasting glucose at baseline and 4 to 6 weeks after the dosage is stabilized Repeat ALT/AST every 12 weeks thereafter for the first year, then every 6 to 12 months Discontinue if ALT or AST is greater than three times normal range or if myopathy or myositis occurs	~$5–$15
Combination Product of Extended-Release Niacin and Lovastatin (Advicor)	• 500-mg niacin and 20-mg lovastatin • 750-mg niacin and 20-mg lovastatin • 1,000-mg niacin and 20-mg lovastatin	Same monitoring parameters for extended-release niacin and lovastatin products	$44–$57
Bile Acid Binding Resins			
Cholestyramine (Questran)	Start: 4 g daily in two or three divided doses; increase at 4-week intervals as tolerated Max: 24 g daily	Check lipid profile for response at 4 weeks Monitor for constipation If constipation occurs, increase fluid and fiber intake, consider stool softener (or laxative)	$55–$330
Colestipol (Colestid)	Start: 5 g daily in two or three divided doses; increase at 4-week intervals as tolerated Max: 30 g daily	Check lipid profile for response at 4 weeks Monitor for constipation If constipation occurs, increase fluid and fiber intake, consider stool softener (or laxative)	$52–$312

Table 11 *continued*

Dosing, Monitoring, and Cost* of Lipid-Lowering Agents



mized during sleep.

Pharmacists should refer patients who are self-medicating with niacin to their primary care provider so that appropriate monitoring can be initiated. Given that many niacin products are available OTC, pharmacists have an important role in ensuring appropriate use of this therapy. Patients should be counseled on how to manage symptoms associated with niacin's vasodilatory effects and instructed to minimize gastrointestinal effects by taking it with food.[64] Any symptoms associated with hepatotoxicity should be reviewed.

Bile Acid Resins

Cholestyramine and colestipol are two of the BARs currently available. A new bile acid sequestrant, colesevelam hydrochloride (Welchol), was approved in May 2000 by the FDA. These agents bind cholesterol and bile acids in the intestinal lumen and prevent their reabsorption, causing the liver to increase its uptake of circulating LDL through an increase in LDL receptors.[42] BARs are moderately effective at lowering LDL levels, and they slightly raise HDL (Table 8). Uncommonly, an increase in serum triglyceride values may be seen. The Lipid Research Clinics Coronary Primary Prevention Trial established that cholestyramine therapy significantly decreases coronary events.[6] BARs are seldom used as initial therapy because success is often limited by poor patient tolerance.[17]

Adverse Effects

Approximately one third of patients will not take the full prescribed dosage because of constipation or poor palatability.[17] Common gastrointestinal disturbances with BARs include nausea, indigestion, bloating, diarrhea, and flatulence.[42] This class of medications is not recommended for use in patients with severe chronic constipation or bowel disease. Concomitant administration of BARs may interfere with intestinal absorption of the fat-soluble vitamins (ie, K, A, D, and E) and numerous medications, including levothyroxine, warfarin, thiazide diuretics, and digoxin (Table 10).[42] Despite the undesirable side-effect profile, BARs have an excellent safety profile because they are not absorbed.[2,3]

Indications

The principal indication for therapy with a BAR is to further reduce serum LDL concentrations in patients who are already receiving a statin.[52] If they are used for monotherapy, they should be restricted to patients with hypercholesterolemia but not hypertriglyceridemia.[52]

Dosing and Monitoring

Gastrointestinal side effects may be minimized by increasing the dosage of the BAR slowly, along with increasing fluid intake and taking stool softeners (Table 11).[42,52] Patients should be instructed to mix the BAR in cold liquids such as pulpy fruit juices to increase palatability. Alternatively, they may be mixed with soft foods (eg, apple sauce, nonfat yogurt, and oatmeal) but not carbonated beverages. The total daily dose can be premixed and stored in the refrigerator (advise the patient to shake or stir well before each use). Other medications should be administered 2 hours before or 4 hours after the BAR.[8]

Fibrates

The fibric acid derivatives available in the United States include gemfibrozil (Lopid) and fenofibrate (Tricor). Fibrates are mainly used to treat hypertriglyceridemia and to increase HDL cholesterol (Table 8).[2,3,50]

Fenofibrate was recently approved by the FDA to reduce LDL levels, but the effects of fibrates on LDL can be variable.[50] The Helsinki Heart Study established that gemfibrozil therapy significantly decreases coronary events.[8] The effects of fenofibrate on CHD have not been evaluated.

Adverse Effects

The most common adverse effects associated with fibrate therapy are gastrointestinal, including abdominal pain, nausea, vomiting, diarrhea, constipation, and dyspepsia.[42] Neuromuscular effects (eg, headache, dizziness, vertigo, and arthralgias) and dermatologic reactions have also been reported.[42] Fibrates increase biliary cholesterol concentrations and can cause gallstones.[42,52] Monotherapy with a fibrate is rarely associated with myalgias or rhabdomyolysis.[42] The incidence significantly increases, however, with comcomitant use of a statin.[42,51] For this reason, extreme caution should be used when these agents are used together (Table 10).

Indications

The main indications for fibrate therapy are serum triglyceride concentrations >1,000 mg/dL (or >400 mg/dL in higher risk patients) and low HDL concentrations.[2,3,52]

The Pharmacist's Role

Although advances have been made in the prevention of CHD through lipid-lowering therapy, CHD remains the leading cause of death in the United States. Pharmacists can contribute improved lipid therapy outcomes with thorough knowledge of cholesterol-lowering medications and current clinical guidelines. With appropriate training, resources, and access to patient data and in collaboration with physicians and other health care providers, pharmacists have demonstrated successful management of lipid disorders.

Formal dyslipidemia management services are not required to positively impact the care of patients receiving antihyperlipidemic therapy. Patients at risk for CHD should be closely monitored with regard to lifestyle modifications and compliance with diet, exercise, and drug therapies. Risk factors for CHD should be identified, with outcome goals clearly explained. Assessment of therapy in relation to lipid reduction should be analyzed and recorded, with attention also paid to control of concomitant disease states, such as hypertension and diabetes.

With the advent of new self-monitoring devices and the use of risk assessment software, which requires simple patient histories and limited physical examination information, pharmacists in collaboration with physicians can help patients to better understand their condition, treatment options, and therapeutic goals. The accessibility of pharmacists places them in an ideal position to play a contributory role in monitoring and managing patients with and at risk for CHD. PT

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. E. McCardell, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: emccardell@pharmacytimes.com.

A 2002 Update: Managing Lipid Disorders

This educational lesson will be available to pharmacists online at www.pharmacytimes.com.
(Based on the article starting on page 65.) Choose the one most correct answer.

1. Which of the following is considered beneficial when assessing risk factors for coronary heart disease (CHD)?
a. low-density-lipoprotein (LDL) cholesterol >160 mg/dL
b. LDL cholesterol >200 mg/dL
c. high-density-lipoprotein (HDL) cholesterol >60 mg/dL
d. HDL cholesterol <60 mg/dL

2. How often should adults over the age of 20 years be screened for hyperlipidemia?
a. annually
b. once every 5 years
c. once every 10 years
d. with each visit to a physician

3. What laboratory follow-up is recommended for a patient with a fasting total cholesterol of 220 mg/dL and two risk factors?
a. perform glucose testing
b. repeat testing within 8 weeks
c. repeat testing within 5 years
d. reevaluate risk status in 1 to 2 years and repeat testing at this time

4. Which of the following laboratory values is most affected by recent food intake?
a. triglycerides
b. total cholesterol
c. LDL cholesterol
d. HDL cholesterol

5. What is the LDL cholesterol goal for patients with existing cardiovascular disease?
a. <200 mg/dL
b. <160 mg/dL
c. <130 mg/dL
d. ≤100 mg/dL

6. Which of the following can contribute to a secondary cause of hyperlipidemia?
a. diabetes
b. hypothyroidism
c. obstructive liver disease
d. all of the above

7. Which of the following statins was withdrawn from the U.S. market in 2001 after fatalities were linked to its use?
a. Baycol
b. Lescol
c. Mevacor
d. Zocor

8. Which of the following clinical outcomes has been shown in large trials using statins in patients with existing CHD?
a. decreased risk of coronary events and deaths
b. decreased risk of mortality from all causes
c. decreased risk of stroke
d. all of the above

9. Which of the following is a common side effect of the statins?
a. acanthosis nigricans
b. nephrotoxicity
c. gastrointestinal disturbances
d. hyperuricemia

10. Which of the following statins is a useful option if cytochrome P-450 drug interactions are a concern?
a. atorvastatin
b. fluvastatin
c. pravastatin
d. simvastatin

11. Which of the following statins produces the greatest reduction in LDL cholesterol?
a. atorvastatin
b. fluvastatin
c. pravastatin
d. simvastatin

12. In addition to the lipid profile, which of the following laboratory values should be monitored before and after starting statin therapy?
a. liver function tests
b. creatine kinase
c. serum uric acid
d. serum glucose

13. Which of the following is not necessary when attempting to reduce the incidence of adverse effects with niacin therapy?
a. take niacin at bedtime
b. avoid taking niacin with alcohol
c. administer the niacin with a warm beverage
d. premedicate with 325 mg of aspirin (if not contraindicated) 30 to 60 minutes before taking niacin

14. Niacin should be used with caution in patients with a history of
a. renal failure
b. peptic ulcer disease
c. congestive heart failure
d. thyroid dysfunction

15. In addition to the lipid profile, which of the following laboratory values should be monitored before and after starting niacin therapy?
a. liver function tests
b. serum uric acid
c. serum glucose
d. all of the above

16. Concomitant administration of which of the following medications with bile acid resins may affect its/their absorption?
a. vitamins K, A, D, and E
b. digoxin
c. warfarin
d. all of the above

17. Common adverse effects associated with fibrate therapy include
a. gastrointestinal intolerance
b. dermatologic reactions
c. neuromuscular reactions
d. myalgias

18. Which of the following lipid-lowering agents produces the greatest reduction in triglycerides?
a. niacin
b. fibrates
c. file acid binding resins
d. statins

19. Which of the following lipid-lowering agents produces the greatest reduction in LDL cholesterol?
a. niacin
b. fibrates
c. bile acid binding resins
d. statins

20. Which of the following lipid-lowering agents produces the greatest increase in HDL cholesterol?
a. niacin
b. fibrates
c. bile acid binding resins
d. statins

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MAYO CLINIC HEALTH INFORMATION

High Blood Cholesterol

Screening & Diagnosis

A good way to detect high blood cholesterol early so that you can take steps to improve your health is to have a regular blood test to measure your cholesterol level. Some doctors recommend having your levels of high-density lipoprotein (HDL) cholesterol — the so-called "good cholesterol" — and of triglycerides, another type of blood lipids, measured initially, as well as your total cholesterol level. A typical blood cholesterol test measures:

- Total cholesterol
- HDL cholesterol
- Triglycerides

Values for low-density lipoprotein (LDL) cholesterol can be calculated from the other three values, providing a good estimate. You usually don't need a precise measurement of your LDL cholesterol level. However, if you do, another blood test to specifically determine your LDL level is used.

Measuring only total cholesterol can be misleading because some people have low levels of HDL cholesterol and high levels of triglycerides, but normal or even high levels of LDL cholesterol. In these cases, a total cholesterol measurement might appear normal. You and your doctor would be unaware of the risk of heart disease posed by the abnormal levels that weren't measured. Even with a desirable total cholesterol level, if you have a low HDL level, you may be at increased risk for heart disease.

Desirable ranges for cholesterol levels vary depending on risk factors such as your age, gender, family history and health condition. There's no magic number that separates risky levels from safe levels. Rather, expert investigators and doctors have identified levels of lipids in the blood above which the risk for developing

coronary complications is high enough to warrant changes. Talk to your doctor about what level is appropriate for you.

Desirable values:

If you're healthy:

- Total cholesterol: Below 200 mg/dl
- Total triglycerides: Below 200 mg/dl
- HDL cholesterol: Above 45 mg/dl
- LDL cholesterol: Below 130 mg/dl

If you have coronary artery disease:

- Total cholesterol: Below 200 mg/dl
- Total triglycerides: Below 200 mg/dl
- HDL cholesterol: Above 35 mg/dl
- LDL cholesterol: Below 100 mg/dl

Have a baseline cholesterol test in your 20s and then every 3 years to 5 years. If your values are not within desirable ranges, your doctor may advise more frequent measurements.

You can also purchase a home cholesterol test. However, these tests measure only total cholesterol, are less sophisticated than laboratory tests and may give unreliable results.

— Last Updated: Aug. 10, 2000

MAYO CLINIC HEALTH INFORMATION

High Blood Cholesterol

Treatment

Lifestyle changes are the first steps to take to improve your blood levels of cholesterol and triglycerides. These steps include changes in diet, exercising regularly and not smoking (see Prevention). But if you've made these important lifestyle changes and your total cholesterol — especially your level of low-density lipoprotein (LDL) cholesterol — remains high, your doctor may recommend prescription medication.

Before recommending medication, your doctor may weigh many variables — your changeable risk factors, your age, your current health, and the drug's side effects. If you need a medication to improve your cholesterol levels, chances are you may need it for many years.

Your LDL cholesterol level is usually the deciding factor. If you have no risk factors for heart disease, an LDL level greater than 190 generally requires medication. With two or more risk factors, an LDL level greater than 160 may require medication. If plaques have narrowed the arteries around your heart and restricted the flow of oxygen-rich blood to your heart's muscles (coronary artery disease), your doctor may try medication and lifestyle changes to lower your LDL to less than 100.

Medications to improve blood cholesterol levels include:

- **Resins.** The medications cholestyramine (Questran) and colestipol (Colestid) lower cholesterol indirectly by binding with bile acids in your intestinal tract. Your liver makes bile acids, which you need for digestion, from cholesterol. By tying up bile acids, resins prompt your liver to make more bile acids. Because your liver uses cholesterol to make bile

acids, there's less cholesterol available to reach your bloodstream.

- **Triglyceride-lowering drugs.** These medications include fibrates such as gemfibrozil (Lopid) and fenofibrate (Tricor), and niacin (nicotinic acid). Fibrates reduce triglyceride production and remove triglycerides from circulation. They often also increase your HDL cholesterol level.

- **Statins.** Statins work directly in your liver to block a substance your liver needs to make cholesterol. This depletes cholesterol in your liver cells, which causes your liver cells to remove cholesterol from your blood. Statins can reduce your LDL cholesterol by up to 40 percent. Statins also may help your body reabsorb cholesterol from plaques that accumulate on the walls of your arteries. This process slowly unplugs your blood vessels. Statins include fluvastatin (Lescol), lovastatin (Mevacor), simvastatin (Zocor), pravastatin (Pravachol), atorvastatin (Lipitor) and cerivastatin (Baycol).

Last Updated: Aug. 10, 2000

- Orlistat — Medication for obesity